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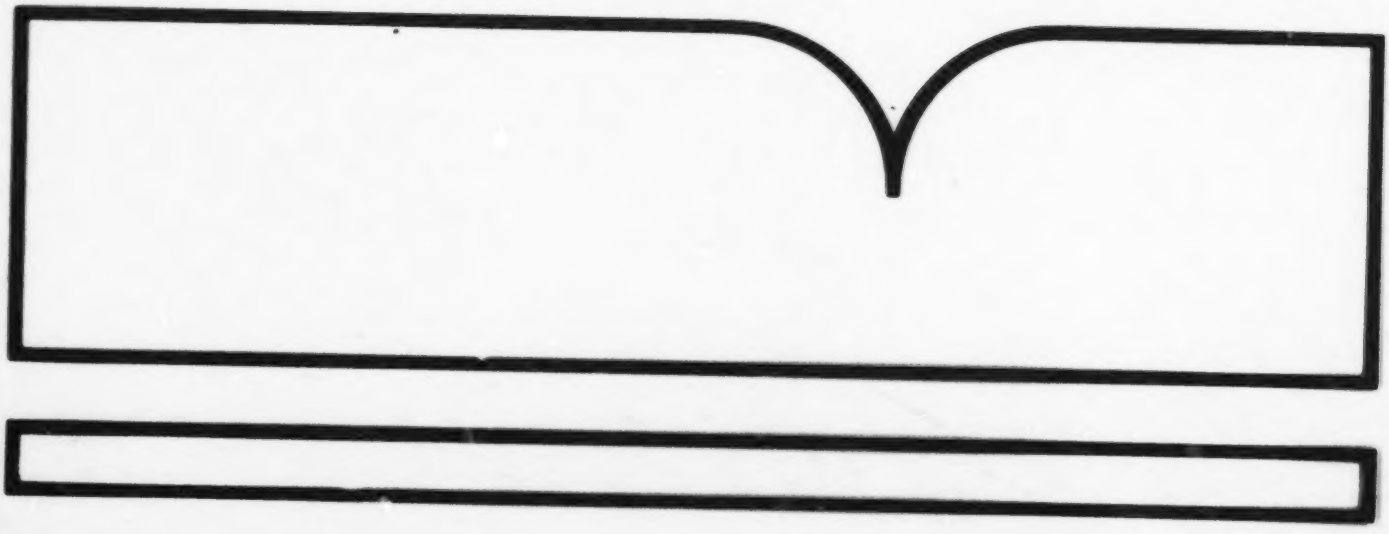

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Commentary

Commentary on 'Cellular, Biochemical and Functional Effects of Ozone: New Research and Perspectives on Ozone Health Effects'

Gary E. Hatch[1], Jeffrey Tepper[2], MaryJane Selgrade[1] and Daniel L. Costa[1]

[1] *Health Effects Research Laboratory, U.S. E.P.A. and* [2] *N.S.I. Tech. Services Inc., Research Triangle Park, NC (U.S.A.)*

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Ozone has received considerable attention recently because the National Clean Air Act is being revised and ozone represents a pollutant that has not been controlled by the previous act. Some expensive measures have been taken to limit atmospheric ozone, many concerned with emission controls on automobiles. Yet despite these efforts, over half of the U.S. population is living in areas where ozone concentrations exceed the National Ambient Air Quality Standard (NAAQS). An effort to develop 'clean' automobile fuels (methanol, etc.) has arisen in large part out of the ozone problem, and it is estimated that clean fuels will cost $3 to $4 billion per year after they are in full use [1], not to mention start-up costs.

Health effects studies on ozone will be of critical importance in evaluating fuel alternatives of the future. Research on effects of inhaled ozone has been intense, and as improved measuring tools have become available, toxicological effects of ozone have been demonstrated at lower and lower exposure concentrations. There is now a large body of data concerned with these health effects [2] and new studies are constantly appearing. We have arrived at the point where health effects of ozone have

Address for correspondence: Gary E. Hatch, Health Effects Research Laboratory, U.S. E.P.A., Research Triangle Park, NC 27711, U.S.A.

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been demonstrated at NAAQS concentrations, yet the economic costs of reducing ozone below the NAAQS is so great, it is being questioned whether the health effects are indeed 'adverse' or whether they are simply a stimulus to which humans can readily adapt.

The review article that follows attempts to extract from the most recent ozone literature some 'generalities' which could put our present knowledge in perspective and guide future research on ozone effects. The central issue, although not clearly stated in the review, is the question of 'adversity'. As the title suggests, the review is more a 'perspective' than a 'review', since it represents a definite viewpoint. The flavor is one of caution that we avoid overstatement of the potential risk because we do not as yet fully understand the adversity question. Another recent review by Dr. Morton Lippman [3] is representative of the other side of the ozone debate which emphasized that the mere detection of health effects at levels that are often encountered in ambient air is reason for concern.

The authors never define explicitly their use of the term 'adverse' but do mention the words 'irreversible (structural defects) with associated decrements in lung function'. We would suggest that although this wording is clearly not arguable, less dramatic impairments must also be considered. A conservative approach is needed given the fact that ozone by its very nature exists in combination with other pollutants, and that considerable variability exists in the exposed human population.

Surely, the word 'toxic' is appropriate for ozone at doses higher than ambient, thus questions of adversity often occur because ambient ozone effects are at the lower end of classical toxicological dose–effect studies. It is accurate to say that considering the full range of the ozone dose response, there is no other identified air pollutant that has the same combination of both high toxic potency and large exposed human population. The following discussion will address questions of interpretation in the areas of ozone-induced pulmonary function decrements, morphological and fibrotic changes, alterations in host defense against infection, and adaptive responses.

Human pulmonary function decrements caused by ozone are discussed in the review with emphasis on the fact that these effects are reversible, they are not mechanistically defined, they are highly variable between subjects, and they are only seen following strenuous exercise in the presence of ozone. In spite of these uncertainties, it is important to realize that these effects are statistically significant in young, healthy subjects even at the NAAQS of 0.12 ppm ozone (6.6 h) [4]. The impact of this type of change would probably be greater in unhealthy subjects which have less reserve capacity. Thus, there appears to be little or no 'margin of safety' (as classically defined) for ozone. In fact, among the exposed group are certain individuals who suffer substantial pulmonary function decrements. Moreover, recent studies done at E.P.A. that will be presented at the 1990 meeting of the American Thoracic Society show that only moderate exercise at levels of ozone well below the NAAQS (0.08 ppm, 6.6 h) induces functional impairments and pulmonary inflammation in healthy human subjects.

The fact that considerable variability exists among individuals suggests that subpopulations might exist that are at increased risk to ozone exposure. Such populations are also guaranteed protection under the Clean Air Act. However, little attention has been given to the possibility of the existence of hypersusceptible individuals. The plausibility of a genetic component to ozone sensitivity has recently been strengthened by studies in which genetic strains of mice have been shown to have increased sensitivity to ozone [5]. With 150 million people in the United States potentially exposed to ozone, even a small fraction of 'responders' could represent many thousands of people.

Considerable emphasis is given in the review to the 'reversibility' of the ozone effects. Only slight attention was given to some of the most convincing evidence that ozone can cause irreversible chronic effects in the lung [6]. There was a morphological thickening of interstitial matrix and basement membranes in the centriacinar region of the lungs of rats that did not reverse itself, but remained 30% above normal, even 4 months after termination of an urban-level chronic exposure. The review seems to minimize this finding by pointing out that in spite of the thickening, the number of collagen fibers did return to normal. A similar point was made in the review that when lung collagen is increased, other proteins are increased as well. In answer to this, we believe that there is not yet a sufficient understanding of the entity called 'fibrosis' to exclude as unimportant those changes in which increases in collagen are accompanied by a general increase in protein synthesis, or to exclude 'thickening' that does not involve collagen fibrils.

The review seems to raise doubts about the relevance of fibrosis in animals to the human situation. Few quantitative indicators are available to detect fibrosis and other chronic lung diseases, and those that are available are quite insensitive. Because of this, our understanding of the development of chronic lung disease in general is very limited and it is not yet possible to 'link' acute toxicity with chronic toxicity, even in animal studies. Compounding this difficulty is the fact that 2-year animal studies which form the basis for our present knowledge of the chronic effects of ozone must be extrapolated to 60+ years of human exposure if we are to discern an adequate margin of safety. Also, the review does not mention that non-fibrotic diseases, although less-studied, need to be considered. There is a possibility that ozone could accelerate the aging of lung tissue [3] and enhance carcinogenic [7] and emphysemic [2] processes.

The effects of ozone on particle clearance from the airways and on alveolar macrophage and lymphocyte function are also reviewed. Noticeably lacking in this discussion is mention of data which show that animals exposed to very low levels of ozone are exquisitely sensitive to subsequent challenge with bacterial aerosols [8,9]. While more work is needed to elucidate the mechanisms involved in this response and hence improve our ability to extrapolate to the human situation, these data clearly are worthy of mention.

A large section of the review addresses the question of 'adaptation'. There is evi-

dence from the literature that functional and perhaps structural adaption to ozone occurs. The suggestion is made that since even pristine areas have measurable ozone, we are all 'adapted' to some extent. More research is needed to define how long the adapted state persists, and whether all effects of ozone are subject to adaptation. Recent evidence suggests that although functional changes may adapt quickly, this belies progressive cellular and morphological change [10]. Adaptation also may figure importantly in the conversion of acute to chronic injury. A recent study showed that when monkeys were exposed monthly (such that adaptive responses might be lost between exposures), more chronic lung effects were seen than when exposure was continuous [11]. While further studies are needed on adaptation, we also need to ask where we would be today if research on the effects of cigarette smoking had emphasized solely the adaptive responses. Clearly, a more important question might be: 'To what extent is adaptation completely effective in preventing long-term effects of ozone?'

In summary, the review that follows includes many salient points on ozone toxicity and raises some interesting questions to be pursued in future research. The review examines some scientific issues which are controversial, particularly those which attempt to interpret whether certain effects of ozone should be considered 'adverse'. We have attempted to offer some modifying views in a spirit of obtaining a balanced picture of the ozone problem. There are significant economic costs for this country and for other countries which will follow in our footsteps in dealing with the ozone problem. Many of the decisions that will be made hinge on interpretation of toxicity data. In view of these factors, we believe that the type of synthesis and interpretation of literature exemplified in this review, with its ensuing discussion, is needed and should be welcomed. (This commentary does not necessarily reflect E.P.A. policy)

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